Copy for the Elected Office (EO/US) PCT/IB00/00837

PATENT COOPERATION TREATY

09/926807

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

GILSON, David, Grant
Spoor and Fisher
P.O. Box 41312
2024 Craighall
AFRIQUE DU SUD

Date of mailing (day/month/year) 28 January 2002 (28.01.02)	
Applicant's or agent's file reference W/U/101	**IMPORTANT NOTIFICATION**
International application No. PCT/IB00/00837	**International filing date** (day/month/year) 22 June 2000 (22.06.00)

1. The following indications appeared on record concerning:
[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:
[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
SOUTH AFRICAN MEDICAL RESEARCH COUNCIL Francie van Zijl Drive 7505 Parow South Africa	ZA	ZA
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
Addition of an applicant for all designated States except US.

4. A copy of this notification has been sent to:
[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Sean Taylor
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

004621904

Form PCT/IB/306 (March 1994)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 March 2001 (08.03.01)	
International application No. PCT/IB00/00837	**Applicant's or agent's file reference** W/U/101
International filing date (day/month/year) 22 June 2000 (22.06.00)	**Priority date** (day/month/year) 24 June 1999 (24.06.99)
Applicant MEYER, Jacobus, Johannes, Marion et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

23 January 2001 (23.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Pascal Piriou

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PA129319/PCT		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/IB00/00837	22/06/2000	24/06/1999

International Patent Classification (IPC) or national classification and IPC
C07C50/12

Applicant
UNIVERSITY OF PRETORIA et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report
   II ☐ Priority
   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☐ Lack of unity of invention
   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   VI ☒ Certain documents cited
   VII ☒ Certain defects in the international application
   VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/01/2001	17.08.2001

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax +49 89 2399 - 4465

Authorized officer
Bueno Torres, M
Telephone No. +49 89 2399 6290

Form PCT/IPEA/409 (cover sheet) (January 1994)

SR22429, 13.08.2001

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB00/00837

I. Basis of the report

1. With regard to the elements of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-14 as originally filed

Claims, No.:

1-11 with telefax of ✓ 29/06/2001

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 6-11.

because:

☒ the said international application, or the said claims Nos. 6-11 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-11
	No:	Claims
Inventive step (IS)	Yes:	Claims 2-5, 7-10
	No:	Claims 1, 6, 11
Industrial applicability (IA)	Yes:	Claims 1-5

No: Claims

2. Citations and explanations
see separate sheet

VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

III. Claims 6-11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V. i) The following documents have been taken into consideration:

D1: KHAN M R ET AL: 'ANTIBIOTIC ACTION OF CONSTITUENTS OF ROOT BARK OF EUCLEA-NATALENSIS.' PAK J SCI IND RES. (1978 (RECD 1979)) 21 (5-6), 197-199. , XP000978450

D2: KHAN, M. R. (1) ET AL: 'Constituents of Diospyros lolin, D. maritima and D. novoguinensis.' FITOTERAPIA, (APRIL, 1999) VOL. 70, NO. 2, PP. 194-196. , XP000978591

D3: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; VICHKANOVA, S. A. ET AL: 'Search for antimicrobial drugs among quinones of plant origin' retrieved from STN Database accession no. 91:83030 XP002157353 & RASTIT. RESUR. (1979), 15(2), 167-77 ,

D4: HAZRA, BANASRI ET AL: 'In vitro antiplasmodial effects of diospyrin, a plant-derived naphthoquinoid, and a novel series of derivatives' PHYTOTHER. RES. (1995), 9(1), 72-4 , XP000978372

D5: YARDLEY, VANESSA ET AL: 'In vitro activity of diospyrin and derivatives against Leishmania donovani, Trypanosoma cruzi and Trypanosoma brucei brucei' PHYTOTHER. RES. (1996), 10(7), 559-562 , XP000978369

D6: HAZRA, BANASRI ET AL: 'Biological activity of diospyrin towards Ehrlich ascites carcinoma in Swiss 'A mice' PLANTA MED. (1984), 50(4), 295-7 , XP000978377

D7:HAZRA, BANASRI ET AL: 'New diospyrin derivatives with improved tumour inhibitory activity towards Ehrlich ascites carcinoma' MED. SCI. RES. (1994), 22(5), 351-3 , XP000978374

D8:ROUSHDI I M ET AL: 'Synthesis of 1,4-naphthoquinones-4-aryl(aroyl)hydrazone s of potential antimicrobial activity.' PHARMAZIE, (1976) 31 (12) 856-9. , XP000971908

D9: OERIU I: 'Relation between the chemical structure and the antitubercular

effect of alpha-naphthoquinone derivatives substituted in 2 and 3 positions.' PHARMAZIE, (1961 MAY) 16 266-72., XP000971910

D10: OERIU I: 'Zusammenhänge zwischen der chemischen Struktur und der antituberkulösen Wirkung der in Stellung 2 und 3 substituieren Derivate des alpha-Naphthochinons' PHARMAZIE,DD,VEB VERLAG VOLK UND GESUNDHEIT. BERLIN, no. 16, 1961, pages 320-327, XP002078405 ISSN: 0031-7144

ii) D1-D2 and D4-D7 do not disclose the antituberculous activity of the compounds of formula 1. Therefore, the subject-matter of claims 1-11 is considered to be novel vis-à-vis D1-D2 and D4-D7.

The subject-matter of claim 1 is novel vis-à-vis D3 mainly on account of the fact that in the compounds of formula 1 R_1 cannot be hydrogen.

D3 and D8-D10 disclose 1-4-Naphthoquinone derivatives having antituberculous activity. However, the compounds of formula 1 as defined in claim 1 have not been disclosed among said 1-4-Naphthoquinone derivatives. The subject-matter of claims 1-11 is therefore novel vis-à-vis D3 and D8-D10.

iii) The closest prior art is considered to be D3 which discloses the compound "plumbagin"in connection with activity against Mycobacterium tuberculosis . The compounds of formula 1 wherein R_2, R_3 and R_4 represent hydrogen (eg 7-methyljuglone) merely differ from "plumbagin" due to the presence of a methyl group at the 7- instead of at the 2-position of the naphthoquinone moiety.

The applicant has argued with his letter of 29.06.01 that minor structural differences may result in large differences in specific activities of these compounds and that the literature in respect of naphthoquinones includes many examples where simple structural changes to the basic naphthoquinone structure have resulted in vastly different activities in respect of their pharmacological properties. The applicant has cited the following references in support of his arguments:

R1: Tikkanen, L. et al: "Mutagenicity of natural naphthoquinones and benzoquinones in the Salmonella/microsome test". Mutation Research, 124 (1983) 25-34.

R2: Mahoney, N et al: Regulation of Aflatoxin Production of Naphthoquinones of Walnut (Juglans regia)" J. Agric. Food Chem. 2000, 48, 4418-4421.

R3: Likhitwitayawuid, K et al: "Antimalarial Naphthoquinones from Nepentes thoarelii" Planta Medica 64 (1998) 237-241.

The data of the activity against Mycobacterium tuberculosis given in the description (see pages 10-12 of the description) merely relate to the compounds diospyrin and methyljuglone. Therefore, having regard for the applicant's arguments and for these results an inventive step can be acknowledged for the subject-matter of claims 2-5 and 7-10. However, said results are not regarded as sufficient in order to support the presence of an activity against Mycobacterium tuberculosis for all the compounds of formula 1 as defined in claims 1 and 6 (Art. 33(3)PCT).

iv) For the assessment of the present claims 6-11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VI. For the purposes of this opinion it has been considered that the priority of date of 24.06.1999 has been validly claimed.

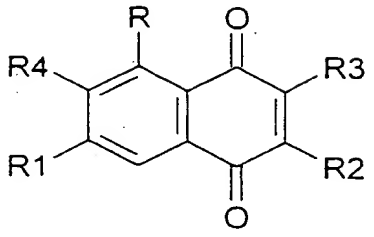
D11: ADENIYI, B. A. ET AL: 'Antibacterial activity of diospyrin, isodiospyrin and bisisodiospyrin from the root of Diospyros piscatoria (Gurke) (Ebenaceae)' PHYTOTHER. RES. (2000), 14(2), 112-117, XP000978371

VII. To meet the requirements of Rule 5.1(a)(ii)PCT, the documents D1-D10 should have been identified in the description and the relevant prior art disclosed therein should have been briefly discussed.

VIII. The terms "similar ether" and "similar aliphatic hydrocarbon derivative" used trough the claims are relative terms and they are not considered to clearly and unambiguously define the subject-matter for which protection is sought with regard to the chemical structure of the compounds encompassed within said definition (Art. 6 PCT).

CLAIMS

1. A naphthoquinone derivative of Formula 1:

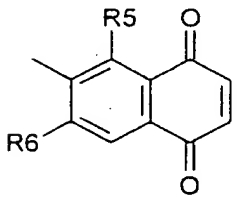


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



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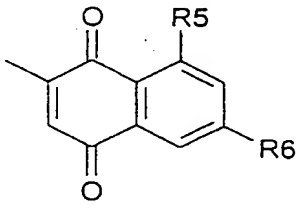
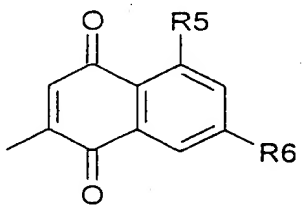
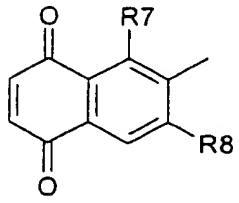


; or



wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:



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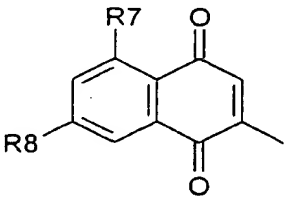
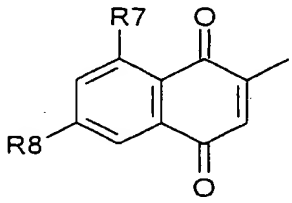


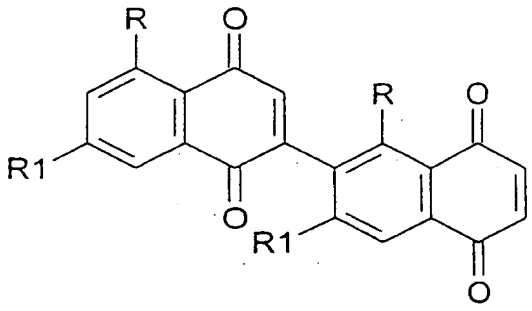
; or



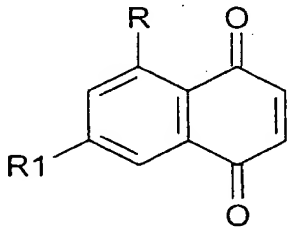
wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

or pharmaceutically acceptable salts thereof, for use in a method of treating and/or controlling tuberculosis in a patient caused by *Mycobacterium tuberculosis*.

2. A naphthoquinone derivative of Formula 1 according to claim 1 which is a compound of Formula 1a or Formula 1b:



Formula 1a



Formula 1b

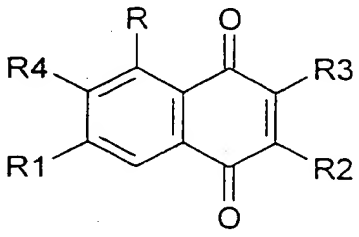
wherein R and R1 are as defined for Formula 1 in claim 1.

3. A naphthoquinone derivative according to claim 2 wherein R is an OH group.

4. A naphthoquinone derivative according to claim 2 or claim 3 wherein R1 is a CH_3 group.

5. A naphthoquinone derivative of Formula 1 according to claim 1 which is 5,5' dihydroxy 7,7' binaphthoquinone (diospyrin) or 5-hydroxy-7-methyl-1,4-naphtoquinone (methyljuglone), or a mixture thereof.

6. The use of a naphthoquinone derivative having the Formula 1:

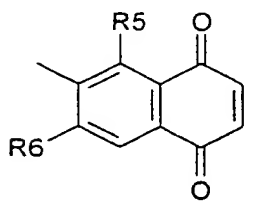


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



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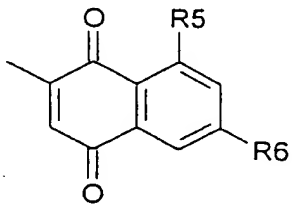
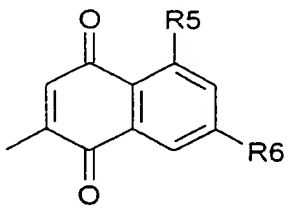
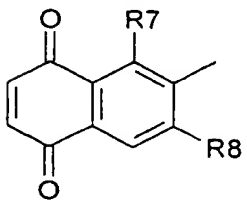


; or



wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:



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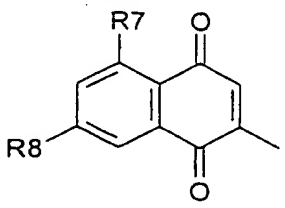
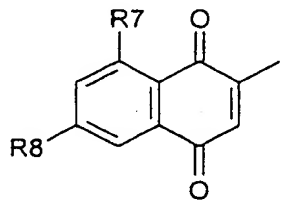


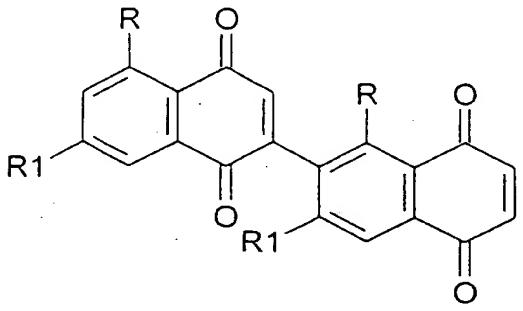
; or



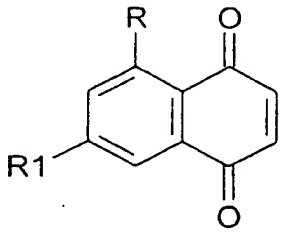
wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for use in a method of treating and/or controlling tuberculosis in a patient caused by *Mycobacterium tuberculosis*.

7. The use according to claim 6 wherein the naphthoquinone derivative of Formula 1 is a compound of Formula 1a or Formula 1b:



Formula 1a



Formula 1b

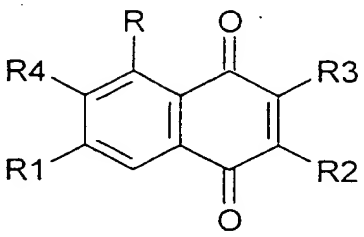
wherein R and R1 are as defined for Formula 1 in claim 6.

8. The use according to claim 7 wherein R is an OH group.

9. The use according to claim 7 or claim 8 wherein R1 is a CH_3 group.

10. The use according to claim 6 wherein the naphthoquinone derivative of Formula 1 is 5,5' dihydroxy 7,7' binaphthoquinone (diospyrin) or 5-hydroxy-7-methyl-1,4-naphtoquinone (methyljuglone), or a mixture thereof.

11. A method of treating and/or controlling tuberculosis caused by *Mycobacterium tuberculosis* comprising administering to a patient in need thereof an effective amount of a naphthoquinone derivative having the Formula 1:

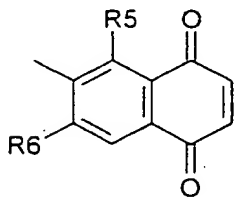


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



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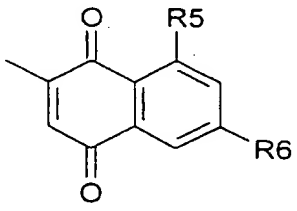

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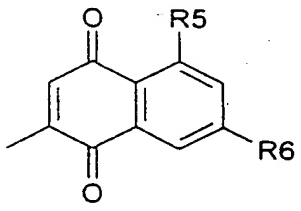
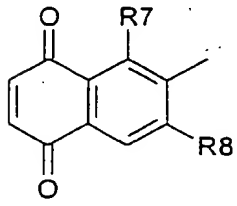


wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:



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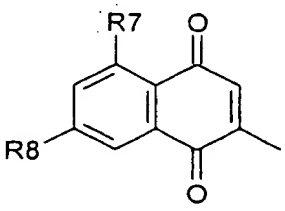

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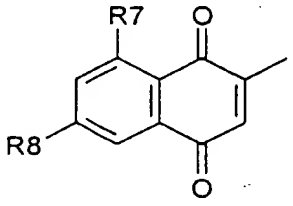
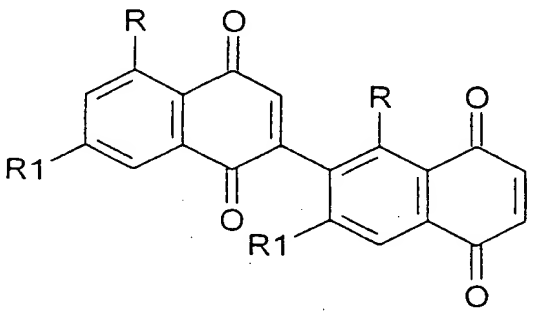


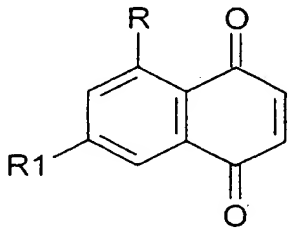
wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

or pharmaceutically acceptable salts thereof.

12. A method according to claim 11 wherein the naphthoquinone derivative of Formula 1 is a compound of Formula 1a or Formula 1b:



Formula 1a



Formula 1b

wherein R and R1 are as defined for Formula 1 in claim 11.

13. A method according to claim 12 wherein R is an OH group.

14. A method according to claim 12 or claim 13 wherein R1 is a CH_3 group.

15. A method according to claim 11 wherein the naphthoquinone derivative of Formula 1 is 5,5' dihydroxy 7,7' binaphthoquinone (diospyrin) or 5-hydroxy-7-methyl-1,4-naphtoquinone (methyljuglone), or a mixture thereof.

16. A method according to claim 11 wherein the naphthoquinone derivative of Formula 1 is administered orally, intravenously, intramuscularly or transdermally.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
W/U/101		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 00/00837	22/06/2000	24/06/1999
Applicant		
UNIVERSITY OF PRETORIA et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

Interna[redacted] Application No
PCT/[redacted] 00/00837

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/122 A61P31/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, BIOSIS, MEDLINE, EMBASE, SCISEARCH, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ADENIYI, B. A. ET AL: "Antibacterial activity of diospyrin, isodiospyrin and bisisodiospyrin from the root of Diospyros piscatoria (Gurke) (Ebenaceae)" PHYTOTHER. RES. (2000), 14(2), 112-117 , XP000978371	1-5
P,Y	the whole document	6-16
X	KHAN M R ET AL: "ANTIBIOTIC ACTION OF CONSTITUENTS OF ROOT BARK OF EUCLEA-NATALENSIS." PAK J SCI IND RES, (1978 (RECD 1979)) 21 (5-6), 197-199. , XP000978450	1-5
Y	the whole document	6-16

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[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 January 2001	26/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, P

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KHAN, M. R. (1) ET AL: "Constituents of Diospyros lolin, D. maritima and D. novoguinensis." FITOTERAPIA, (APRIL, 1999) VOL. 70, NO. 2, PP. 194-196. , XP000978591	1-5
Y	the whole document	6-16
Y	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; VICHKANOVA, S. A. ET AL: "Search for antimicrobial drugs among quinones of plant origin" retrieved from STN Database accession no. 91:83030 XP002157353 abstract & RASTIT. RESUR. (1979), 15(2), 167-77 ,	6-16
Y	ROUSHDI I M ET AL: "Synthesis of 1.4-naphthoquinones-4-aryl(aroyl)hydrazones of potential antimicrobial activity." PHARMAZIE, (1976) 31 (12) 856-9. , XP000971908 abstract	6-16
X	HAZRA, BANASRI ET AL: "In vitro antiplasmodial effects of diospyrin, a plant-derived naphthoquinoid, and a novel series of derivatives" PHYTOTHER. RES. (1995), 9(1), 72-4 , XP000978372	1-5
A	the whole document	6-16
X	YARDLEY, VANESSA ET AL: "In vitro activity of diospyrin and derivatives against Leishmania donovani, Trypanosoma cruzi and Trypanosoma brucei brucei" PHYTOTHER. RES. (1996), 10(7), 559-562 , XP000978369	1-5
A	the whole document	6-16
X	HAZRA, BANASRI ET AL: "Biological activity of diospyrin towards Ehrlich ascites carcinoma in Swiss A mice" PLANTA MED. (1984), 50(4), 295-7 , XP000978377 the whole document	1-5

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HAZRA, BANASRI ET AL: "New diospyrin derivatives with improved tumor inhibitory activity towards Ehrlich ascites carcinoma" MED. SCI. RES. (1994), 22(5), 351-3 , XP000978374 the whole document	1-5
A	OERIU I: "Relation between the chemical structure and the antitubercular effect of alpha-naphthoquinone derivatives substituted in 2 and 3 positions." PHARMAZIE, (1961 MAY) 16 266-72., XP000971910 table 5	1-16
A	OERIU I: "Zusammenhänge zwischen der chemischen Struktur und der antituberkulösen Wirkung der in Stellung 2 und 3 substituieren Derivate des alpha-Naphthochinons" PHARMAZIE,DD,VEB VERLAG VOLK UND GESUNDHEIT. BERLIN, no. 16, 1961, pages 320-327, XP002078405 ISSN: 0031-7144 table 8	1-16

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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WO 01/00554 A2

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(71) Applicant *(for all designated States except US)*: **UNIVERSITY OF PRETORIA** [ZA/ZA]; Corner Lynnwood Road and Roper Street, Hatfield, 0083 Pretoria (ZA).

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(75) Inventors/Applicants *(for US only)*: **MEYER, Jacobus, Johannes, Marion** [ZA/ZA]; 598 Vacy Lyle Street, Elardus Park, 0047 Pretoria (ZA). **LALL, Namrita** [ZA/ZA]; Magnolia Flats 16A, Arcadia, 0083 Pretoria (ZA).

(74) Agent: **GILSON, David, Grant**; Spoor and Fisher, P.O. Box 41312, 2024 Craighall (ZA).

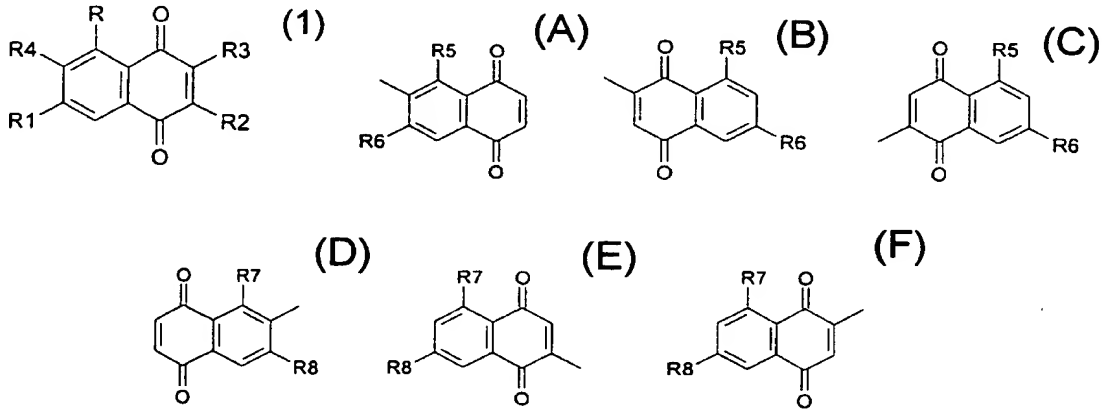
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NAPHTHOQUINONE DERIVATIVES AND THEIR USE IN THE TREATMENT AND CONTROL OF TUBERCULOSIS



(57) Abstract: Naphthoquinone derivatives of Formula (1): wherein, R represents an OH group, methyl ether, ethyl ether or a similar ether; R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative; R2 and R3 each independently represent hydrogen or a group selected from: (A), (B), or (C) wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative; R4 represents hydrogen or a group selected from: (D), (E) or (F) wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative; or pharmaceutically acceptable salts thereof, are useful for the treatment and/or control of a tuberculosis in a patient caused by *Mycobacterium tuberculosis*.

WO 01/00554 A2

NAPHTHOQUINONE DERIVATIVES AND THEIR USE IN THE TREATMENT AND CONTROL OF TUBERCULOSIS

BACKGROUND OF THE INVENTION

THIS invention relates to the treatment and control of tuberculosis caused by *Mycobacterium tuberculosis* and in particular to the use of naphthoquinone derivatives in such treatment and control.

Tuberculosis (TB) remains a serious health problem in many regions of the world, especially in developing nations. It is a contagious disease and is becoming epidemic in some parts of the world. It is estimated that 30-60% of adults in developing countries are infected with *Mycobacterium tuberculosis*. Approximately 8-10 million individuals develop clinical TB and 3 million die of TB each year (WHO/IUATLD, 1989).

In South Africa, over 3 in every thousand people die of TB, the highest rate in the world, while one out of every 200 people suffers from active tuberculosis. Tuberculosis is the most commonly notified disease in South Africa and the fifth largest cause of death among the black population (South African Tuberculosis Association, 1998).

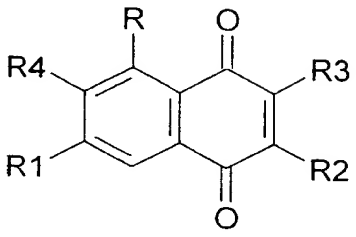
In the United States, the number of TB cases steadily decreased until 1986 when an increase was noted. Since then TB cases have continued to rise. Ten million individuals are infected in the U.S.A., with approximately 26000 new cases of active disease each year (National Jewish Medical and Research Center, 1994).

Individuals infected with Human Immunodeficiency Virus (HIV) are very susceptible to tuberculosis and often develop this disease before other manifestations of AIDS become apparent (Grange and Davey, 1990). Control of the TB epidemic linked with HIV infection will depend largely on the adequate treatment of TB, and possibly of effective chemoprophylaxis, not just for HIV-infected persons but for communities as well (WHO/IUATLD, 1989).

TB therapy has been revolutionized and the present treatment regimes for TB are based on multidrug therapy with usually 3 or 4 antituberculosis drugs. However, the problem of multidrug resistant tubercle bacilli is emerging for various drugs such as isoniazid, ethambutol, rifampicin and streptomycin, for example (Girling, 1989; Grange and Davey, 1990). Drug-resistant TB is very difficult to treat requiring greater numbers and varieties of medications for a longer period of treatment. The need for new antituberculosis agents is urgent due to the increasing resistance of mycobacteria to these classic antituberculosis drugs. A recent WHO report states that, globally, 2% of all cases of tuberculosis are multidrug resistant - by definition, resistance to rifampicin plus isoniazid (plus/minus other resistances). Such cases can be treated in the USA and other high resource regions but at a great cost (> US$ 250,000 per case!) and using very long courses of rather toxic drugs, thereby raising serious problems of compliance (WHO, 1997). South Africa is witnessing an explosion in the number of cases of drug-resistant tuberculosis. In some parts of South Africa, 1 in 10 cases of TB is resistant to treatment (New Scientist, March 1997). It is essential to have new antituberculosis agents, preferably those that can readily and simply be produced from some local source.

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided a naphthoquinone derivative of Formula 1:

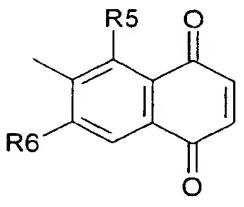


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



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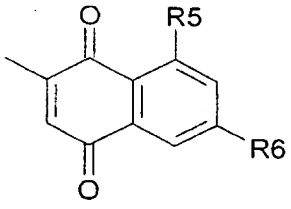

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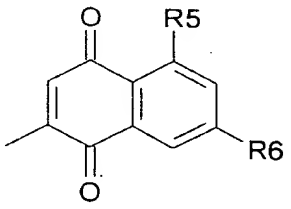
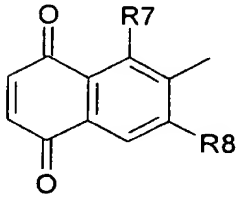


wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:



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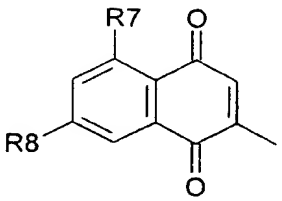

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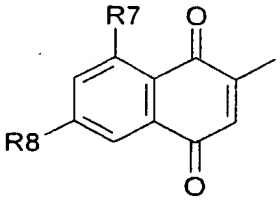


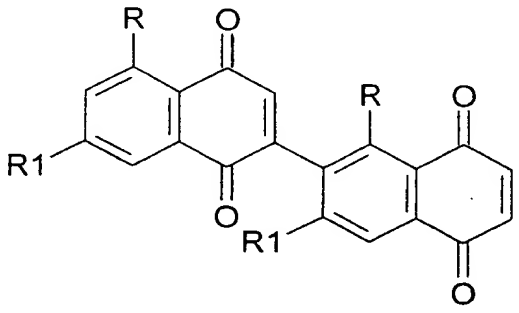
wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

or pharmaceutically acceptable salts thereof, for use in a method of treating and/or controlling tuberculosis in a patient caused by *Mycobacterium tuberculosis*.

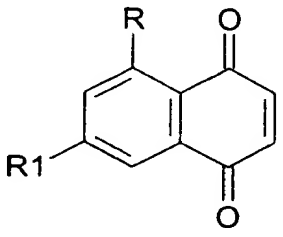
According to a second aspect of the invention there is provided the use of a naphthoquinone derivative having the Formula 1 as set out above in the manufacture of a medicament for use in a method of treating and/or controlling tuberculosis in a patient caused by *Mycobacterium tuberculosis*.

According to a third aspect of the invention there is provided a method of treating and/or controlling tuberculosis caused by *Mycobacterium tuberculosis* comprising administering to a patient in need thereof an effective amount of a naphthoquinone derivative having the Formula 1 as set out above.

The naphthoquinone derivative of Formula 1 is typically a compound of Formula 1a or Formula 1b:



Formula 1a



Formula 1b

wherein R and R1 are as defined for Formula 1 above.

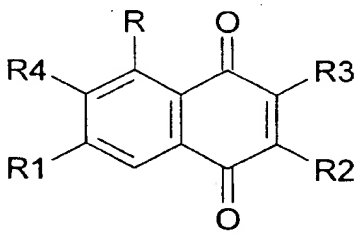
R in the compound of Formula 1a or 1b is preferably an OH group.

R1 in the compound of Formula 1a or 1b is preferably a CH_3 group.

In particular, the naphthoquinone derivative of Formula 1 is 5,5' dihydroxy 7,7' binaphthoquinone (diospyrin) or 5-hydroxy-7-methyl-1,4-naphtoquinone (methyljuglone).

DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is directed at the use of naphthoquinone derivatives in the treatment and/or control of tuberculosis caused by *Mycobacterium tuberculosis*. In particular, naphthoquinone derivatives of the general Formula 1

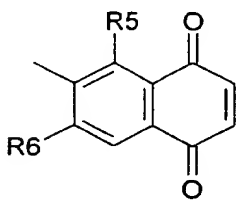


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



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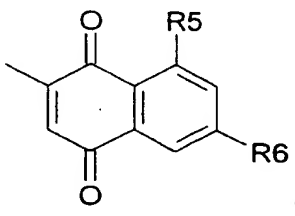

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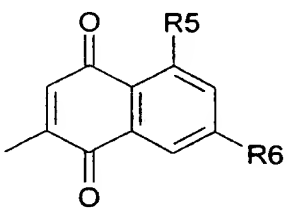
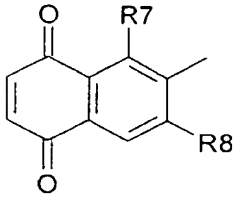


wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:



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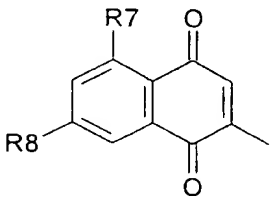

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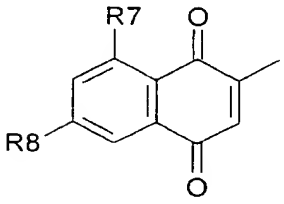
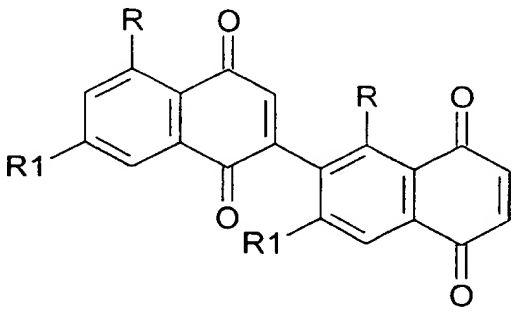


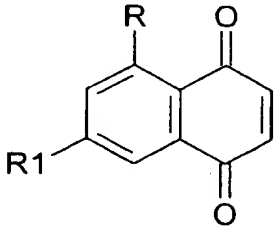
wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

have been found to be effective against *Mycobacterium tuberculosis*.

Particular naphthoquinone derivatives of Formula 1a and 1b have been found to be particularly effective:



Formula 1a



Formula 1b

In particular diospyrin and methyljuglone, naphthoquinone derivatives of Formula 1a and Formula 1b, respectively, in which R is OH and R1 is a methyl group, have been found to inhibit several antibiotic resistant as well as antibiotic susceptible strains of *Mycobacterium tuberculosis*. Although diospyrin and methyljuglone are particularly preferred, naphthoquinone derivatives of Formula 1a and 1b in which R is a methyl ether, ethyl ether or similar ether and R1 is an ethyl or similar aliphatic hydrocarbon derivative are also provided.

An extensive research program was undertaken in order to identify anti-tuberculosis agents that can readily and simply be produced from local resources.

Twenty South African medicinal plants used to treat pulmonary diseases were screened for activity against drug-resistant and sensitive strains of *M. tuberculosis*. A preliminary screening of acetone and water plant extracts, against a drug-sensitive strain of *M. tuberculosis*; H37Rv, was carried out by the agar plate method. Fourteen of the 20 acetone extracts showed inhibitory activity at a concentration of 0.5 mg/ml against this strain. Acetone as well as water extracts of *Cryptocarya latifolia*, *Euclea natalensis, Helichrysum melanacme, Nidorella anomala* and *Thymus vulgaris* inhibited the growth of *M. tuberculosis*. Given the activity of 14 acetone extracts at 0.5 mg/ml against the drug-sensitive strain by the agar plate method a further study was carried out employing the rapid radiometric method to confirm the inhibitory activity. These active acetone extracts were screened against the H37Rv strain as well as a strain resistant to the drugs, isoniazid and rifampicin. The minimal inhibitory concentration of *Croton pseudopulchellus, Ekebergia capensis, Euclea natalensis, Nidorella anomala* and *Polygala myrtifolia* was 0.1 mg/ml against the H37Rv strain by the radiometric method. Extracts of *Chenopodium ambrosioides, Ekebergia capensis, Euclea natalensis, Helichrysum melanacme, Nidorella anomala* and *Polygala myrtifolia* were

active against the resistant strain at 0.1 mg/ml. Eight plants showed activity against both the strains at a concentration of 1.0 mg/ml.

The following procedure was developed by the applicant for the isolation of diospyrin and methyljuglone from *E. natalensis* and other species in this genus, as well as any other plants that may synthesise diospyrin or methyljuglone or other quinone derivatives.

1. **Identification of plant species**

   Roots and the aerial plant parts of *E. natalensis* were collected near Durban and identified at the HGWJ Schweickerdt Herbarium of the University of Pretoria and also at the herbarium of the National Botanical Institute, Pretoria.

2. **Extraction**

   Dried roots of *E. natalensis* were ground to a powdery form with a dry mill and extracted over 48 hours with acetone. The extract was filtered and concentrated to dryness at reduced pressure on a rotary evaporator.

3. **Thin layer chromatography**

   A direct antibacterial bioassay (Dilika & Meyer 1996) on TLC-plates was employed to speedup the activity guided isolation of the antituberculosis compounds. *M. tuberculosis* cannot be tested in this way because of its very slow growth rate. The direct antibacterial bioassays of the acetone extract were done on TLC plates (Merck) developed with chloroform-hexane (1:1). After development, the TLC plates were dried and sprayed with a 24 hr old *Staphylococcus aureus* culture in nutrient broth. After 24 hr incubation, the plates were sprayed with an aqueous solution of 2mg/ml p-iodonitrotetrazolium violet to visualise the bacterial cells. The plates were then reincubated at 37^{0}C for 2-3 hours.

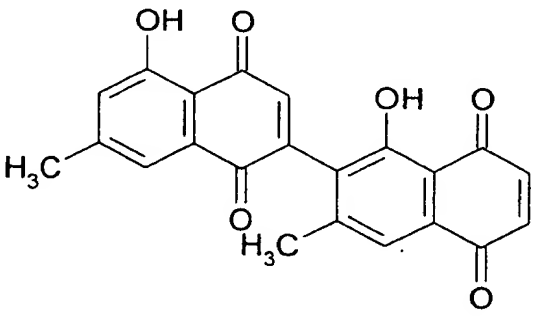
Two zones of bacterial growth inhibition could be seen on TLC plates sprayed with *S. aureus*. Activity was more pronounced in the R_f 0.30 zone (chloroform-hexane (1:1)) than in the R_f 0.54 zone.

4. Column chromatography

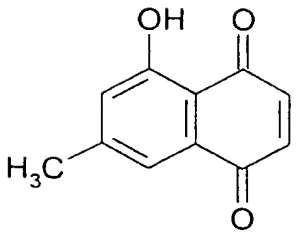
The crude extract of the plant was dried, its mass determined and resuspended in chloroform. Column chromatography was performed on silica gel 60 using chloroform as eluent. The antibacterial fractions collected were then subjected to a Sephadex LH-20 column chromatography using ethanol as eluent. The fractions collected were again tested for antibacterial activity on TLC to detect the fractions containing the active compounds of R_f 0.30 and R_f 0.54.

5. High performance liquid chromatography

The compounds were further purified by HPLC utilising an analytical Phenomenex reverse phase 250x4.60 mm column, at a flow rate of 1.0 ml/min, oven temp. 40^{0}C and a wavelength of 206nm. An ethanol-water (50:50) solution was employed as mobile phase. The pure compounds were once again subjected to a Sephadex LH-20 column chromatography and proved to be pure. The chemical structures were confirmed by ^{1}H and ^{13}C nmr and ms to be:



Diospyrin (5,5' dihydroxy 7,7' binaphthoquinone); $C_{22}H_{14}O_6$. Molecular weight: 374.35



7-methyljuglone (5-hydroxy-7-methyl-1,4-naphtoquinone); $C_{11}H_8O_3$
Molecular weight: 188.19

The effect of diospyrin and methyljuglone on the growth of the sensitive strain (H37Rv) and resistant strains of *Mycobacterium tuberculosis* as determined by the radiometric method are set out in Table 1 and Table 2.

TABLE 1

Effect of diospyrin on the growth of the sensitive strain (H37Rv) and resistant strains of *Mycobacterium tuberculosis* as determined by the radiometric method.

Mycobacterium tuberculosis strains	MIC (mg/ml)	ΔGI[a] values of plant extracts (mg/ml)	ΔGI values of the control vial (mg/ml)
H37 sensitive strain	0.1	-1 ± 1.41	20 ± 4.24
2 drug resistant strain (res. to Isoniazid and rifampicin).	0.1	3.5 ± 0.70	25 ± 7.07
3 drug resistant strain (res. to streptomycin, isoniazid and ethambutol),	0.1	4 ± 2.12	29 ± 1.41

4 drug resistant strain (res. to streptomycin, isoniazid, rifampicin and ethambutol).	0.1	5 ± 2.82	25 ± 2.82
5 drug resistant strain.(res to isoniazid, streptomycin, rifampicin, thiacetazone and cyclocerine).	0.1	10 ± 1.41	22.5 ± 3.53
6 drug resistant strain (res. to isoniazid, rifampicin, ethionamide, terizidone, thiacetazone and ofloxacin).	0.1	9 ± 2.82	30 ± 1.0
7 drug resistant strain.(res to isoniazid, streptomycin, ethambutol, kanamycin, rifampicin, and ethionamide)	0.1	13.5 ±3.2	28 ± 3.1

[a] ΔGI values are means ± s.d.

TABLE 2

Effect of 7-methyljuglone as a single agent and in combination with diospyrin on the growth of the sensitive strain (H37Rv) and resistant strains of *Mycobacterium tuberculosis* as determined by the radiometric method.

Mycobacterium tuberculosis strains	Lab reference no.	Compound(s)	MIC[a] (μg/ml)	ΔGI[b] values of plant extracts	ΔGI values of the control vial
H37Rv sensitive strain	ATCC27294	7-methyljuglone	50	0 ± 1	15 ± 3.78
Two drug (isoniazid and rifampicin) resistant strain	CCKO28469V	7-methyljuglone	50	0 ± 0	30 ± 4.94

H37Rv sensitive strain	ATCC27294	Diospyrin + 7-methyljuglone	10	3 ± 1	15 ± 3.78
Two drug (Isoniazid and rifampicin resistant strain)	CCKO28469V	Diospyrin + 7-methyljuglone	10	3.33 ± 3.05	30 ± 4.94

[a]Minimal inhibitory concentration

[b]ΔGI values are means ± s.d.

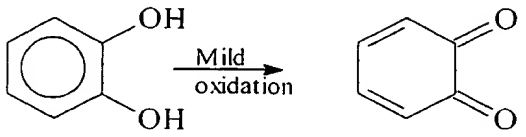
The results show that diospyrin and methyljuglone control the *Mycobacterium tuberculosis* bacterium effectively. Oral administration of diospyrin or methyljuglone in an appropriate pharmaceutical composition with suitable diluents and carriers will typically be used to treat or control tuberculosis. This will be by way of tablet, liquid or similar oral dosage form, as diospyrin and methyljuglone are readily absorbed intestinally.

However, it is believed that diospyrin or methyljuglone administered intravenously or intramuscularly will also be absorbed effectively through blood vessels and the blood stream of a patient. Transdermal administration, via a plaster or similar transdermal administration vehicle, is also a possibility.

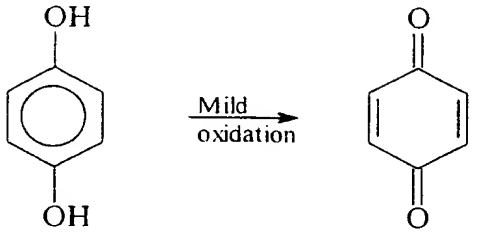
A combination treatment of diospyrin and methyljuglone, which may be more effective than singular treatments of the two naphthoquinones, is also envisaged.

The applicant believes that it may be possible to increase the concentration of diospyrin, methyljuglone and other quinones in *E. natalensis* or similar species by phytoalexic stimulation or by the biotechnological manipulation of tissue cultures and/or intact plants.

Quinones are generally synthesised from catechol (1,2-quinones) or hydroquinone (1,4-quinones) by mild oxidation.

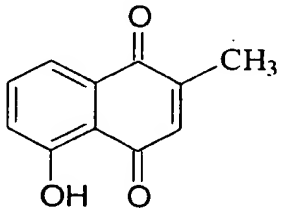


Catechol



Hydroquinone

As far as the applicant has been able to establish, diospyrin has been synthesised once in a laboratory (Yoshida, M and Mori, K. 2000. European Journal of Organic Chemistry pages 1313 – 1317). However, similar binapthoquinones can also be synthesised by the reaction of plumbagin (94mg in methanol, 10ml) and its hydroquinone (190mg in methanol, 14ml), buffered in phosphate to pH 6.8 at 30°C. (Sankaram et al. 1975; Kumari et al. 1982).

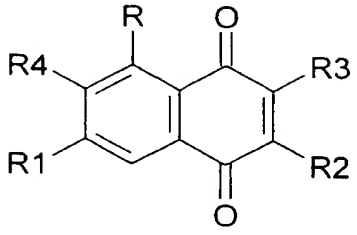


Plumbagin

It is believed that diospyrin, methyljuglone and related naphthoquinone derivatives are viable alternatives to conventional drugs in the treatment and control of tuberculosis in humans.

CLAIMS

1. A naphthoquinone derivative of Formula 1:

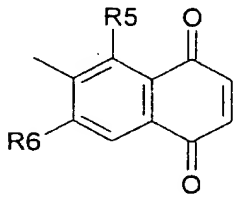


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



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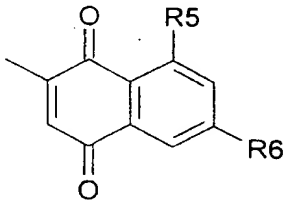

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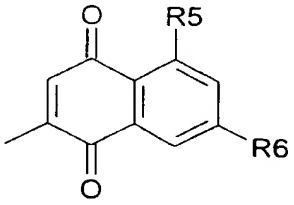
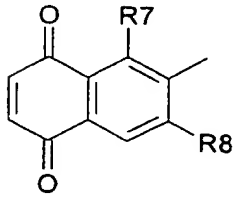


wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:



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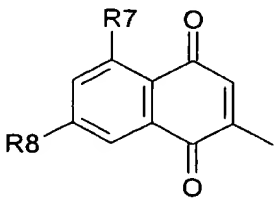

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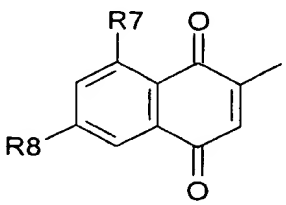
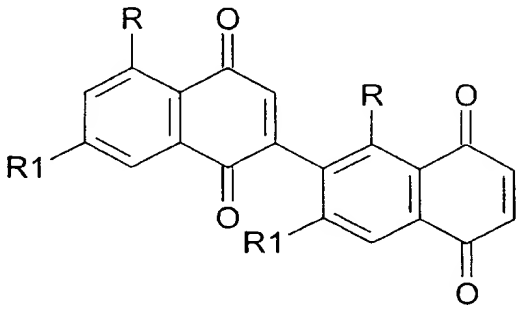


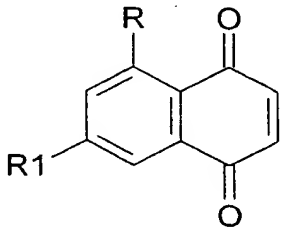
wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

or pharmaceutically acceptable salts thereof, for use in a method of treating and/or controlling tuberculosis in a patient caused by *Mycobacterium tuberculosis*.

2. A naphthoquinone derivative of Formula 1 according to claim 1 which is a compound of Formula 1a or Formula 1b:



Formula 1a



Formula 1b

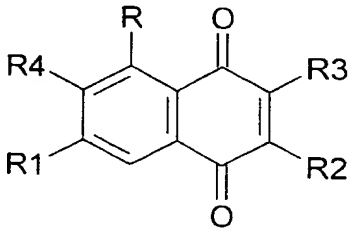
wherein R and R1 are as defined for Formula 1 in claim 1.

3. A naphthoquinone derivative according to claim 2 wherein R is an OH group.

4. A naphthoquinone derivative according to claim 2 or claim 3 wherein R1 is a CH_3 group.

5. A naphthoquinone derivative of Formula 1 according to claim 1 which is 5,5' dihydroxy 7,7' binaphthoquinone (diospyrin) or 5-hydroxy-7-methyl-1,4-naphtoquinone (methyljuglone), or a mixture thereof.

6. The use of a naphthoquinone derivative having the Formula 1:

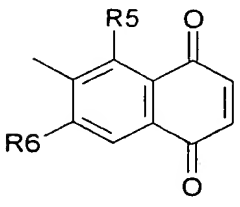


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



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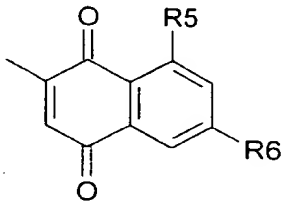

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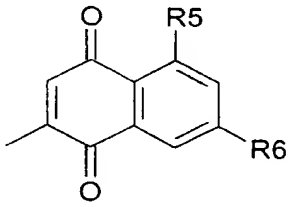
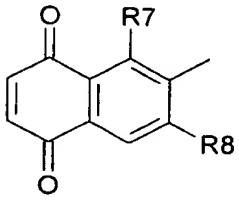


wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:



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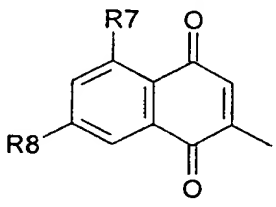
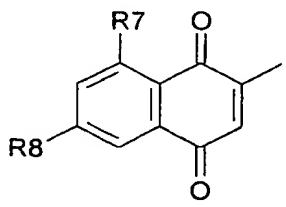


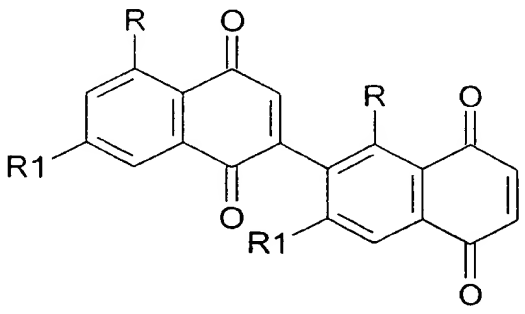
; or



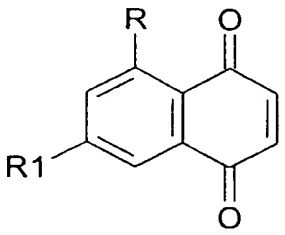
wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for use in a method of treating and/or controlling tuberculosis in a patient caused by *Mycobacterium tuberculosis*.

7. The use according to claim 6 wherein the naphthoquinone derivative of Formula 1 is a compound of Formula 1a or Formula 1b:



Formula 1a



Formula 1b

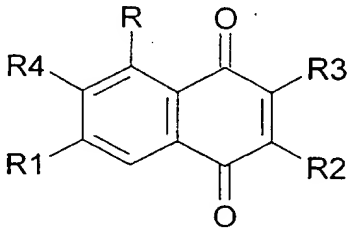
wherein R and R1 are as defined for Formula 1 in claim 6.

8. The use according to claim 7 wherein R is an OH group.

9. The use according to claim 7 or claim 8 wherein R1 is a CH_3 group.

10. The use according to claim 6 wherein the naphthoquinone derivative of Formula 1 is 5,5' dihydroxy 7,7' binaphthoquinone (diospyrin) or 5-hydroxy-7-methyl-1,4-naphtoquinone (methyljuglone), or a mixture thereof.

11. A method of treating and/or controlling tuberculosis caused by *Mycobacterium tuberculosis* comprising administering to a patient in need thereof an effective amount of a naphthoquinone derivative having the Formula 1:

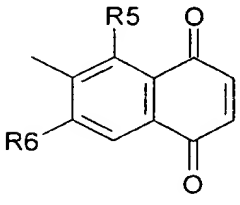


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



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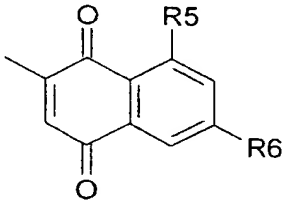

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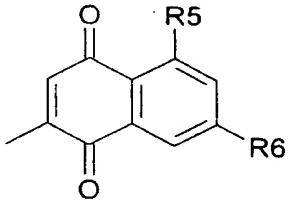
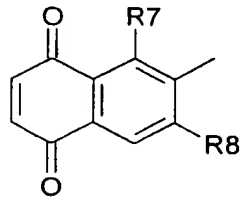


wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:



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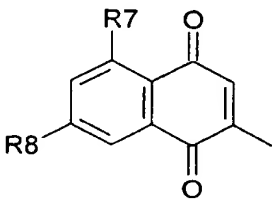
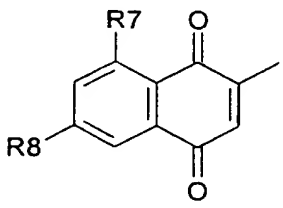
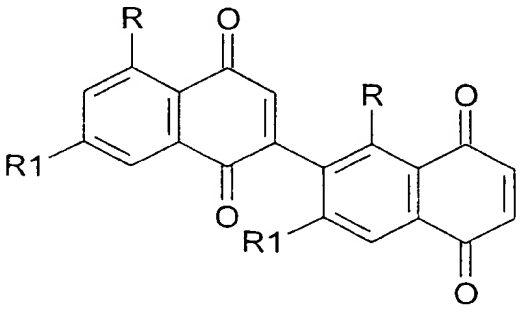


; or


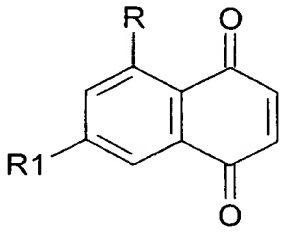
wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

or pharmaceutically acceptable salts thereof.

12. A method according to claim 11 wherein the naphthoquinone derivative of Formula 1 is a compound of Formula 1a or Formula 1b:



Formula 1a



Formula 1b

wherein R and R1 are as defined for Formula 1 in claim 11.

13. A method according to claim 12 wherein R is an OH group.

14. A method according to claim 12 or claim 13 wherein R1 is a CH_3 group.

15. A method according to claim 11 wherein the naphthoquinone derivative of Formula 1 is 5,5' dihydroxy 7,7' binaphthoquinone (diospyrin) or 5-hydroxy-7-methyl-1,4-naphtoquinone (methyljuglone), or a mixture thereof.

16. A method according to claim 11 wherein the naphthoquinone derivative of Formula 1 is administered orally, intravenously, intramuscularly or transdermally.